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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : B05B 17/04	A1	(11) International Publication Number: WO 00/58022 (43) International Publication Date: 5 October 2000 (05.10.00)

(21) International Application Number: PCT/IL00/00181

(22) International Filing Date: 23 March 2000 (23.03.00)

(30) Priority Data:
129208 28 March 1999 (28.03.99) IL

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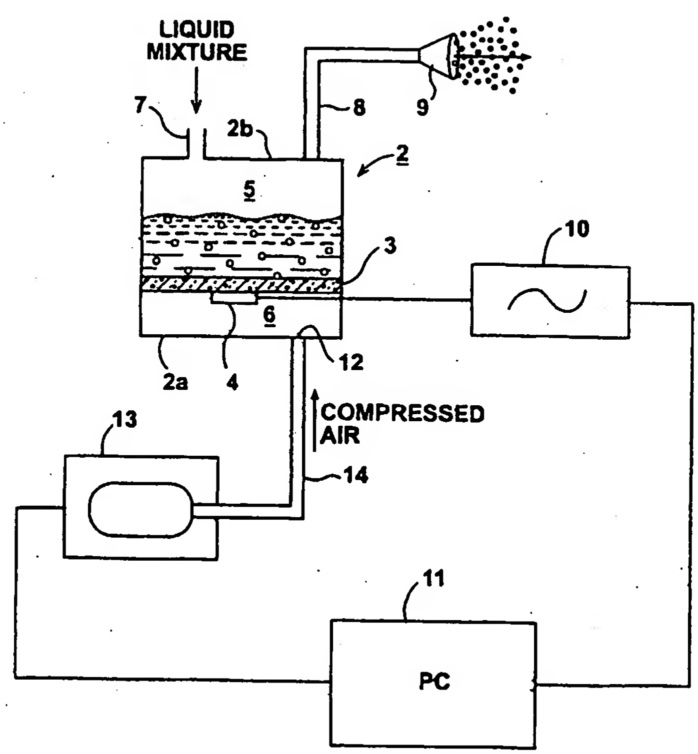
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A METHOD AND APPARATUS FOR NEBULIZING A LIQUID PARTICULARLY USEFUL FOR THE AEROSOL DELIVERY OF BIOPHARMACEUTICALS

(57) Abstract

A method and apparatus for nebulizing a liquid to produce a small-particle aerosol. Liquid to be nebulized is introduced into a reservoir (2) containing a rigid porous body (3), to contact the upper face of the rigid porous body. Pressurized gas is applied to the lower face of the rigid porous body (3) and the rigid porous body is vibrated at an ultrasonic frequency.



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A METHOD AND APPARATUS FOR NEBULIZING A LIQUID PARTICULARLY USEFUL FOR THE AEROSOL DELIVERY OF BIOPHARMACEUTICALS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a method and apparatus for nebulizing a liquid to produce a small-particle aerosol. The invention is particularly useful for the aerosol delivery of biopharmaceuticals, and is therefore described below with respect to this application.

Many techniques are known for nebulizing liquids. In one technique, high pressure air is forced through a nozzle to exit in the form of a high-velocity jet which creates a low-pressure region, causing the liquid to be nebulized to rise in a feed tube and to be sheared into droplets. Such a nebulizer, however, is not suitable for the aerosol delivery of biopharmaceuticals since it produces high shear stresses which degrade or destroy the pharmaceuticals within the droplets. In addition, the resulting droplets cover a wide range of particle sizes.

Another known technique is a bubbling technique, in which bubbles are formed by passing air through a medium-velocity fretted disc immersed in the liquid near the bottom of the reservoir, to produce bubbles which burst and are dried by tangential injection of drying air. As a result, the droplets rapidly shrink in size and are carried out of the generator in an upward swirlingly motion. A drawback of such an aerosol generator, however, is the difficulty in controlling the size distribution range of the particles in the aerosol.

Other known techniques are based on the ultrasonic generation of aerosols by an ultrasonic transducer, such as a pizeoelectric device driven at ultrasonic frequencies. In one type generator, the piezoelectric device is submerged in the liquid to be nebulized and its ultrasonic vibrations produce bubbles which burst and are dried by air, similar to the bubble type generator. In another type generator, the

piezoelectric device is mounted on a main body and disperses the liquid in small droplets through a central hole, or through a perforated membrane having an array of holes. Examples of the later types are described in US Patents 4,850,534, 5,152,456, and 5,261,601. Such piezoelectric type generators, however, also suffer from one or more of the foregoing drawbacks, particularly the production of shear stresses and the difficulty in controlling the particle size distribution.

OBJECTS AND BRIEF SUMMARY OF THE INVENTION

An object of the present invention is to provide a method and apparatus for nebulizing liquids having advantages in the above respects. More particularly, an object of the present invention is to provide a method and apparatus for nebulizing liquids which produce relatively low stresses in the particles of the produced aerosol, and which also permit close control of the particle size distribution, such as to make the method and apparatus especially (but not exclusively) useful for the aerosol delivery of biopharmaceuticals.

According to one aspect of the present invention, there is provided a method for nebulizing a liquid to produce a small-particle aerosol, comprising: providing a reservoir with a rigid porous body; introducing liquid to be nebulized into the reservoir to contact the upper face of the rigid porous body; introducing a pressurized gas to be applied to another face of the rigid porous body; and vibrating the rigid porous body at an ultrasonic frequency.

According to a preferred important feature of the novel method, the rigid porous body is a microporous body having pores of micron size, up to several hundred microns in size. Preferably, the rigid porous body is a ceramic, glass, or a metal.

According to further features in the described preferred embodiments, the rigid porous body is vibrated by

a pizeoelectric mechanism. Preferably, the rigid porous body is vibrated by a pizeoelectric device in contact with the rigid porous body. The rigid porous body may also be vibrated by a pizeoelectric material incorporated in a porous matrix and integrated with the rigid porous body according to known techniques as will be described more fully below.

According to another aspect of the present invention, there is provided an aerosol generator for nebulizing a liquid to produce a small-particle aerosol, comprising: a reservoir for receiving liquid to be nebulized; a rigid porous body within the reservoir; a liquid inlet for introducing liquid to be nebulized into the reservoir to contact the upper face of the rigid porous body therein; a source of pressurized gas for introducing a pressurized gas into the reservoir to be applied to another face of the rigid porous body; and a vibrator for vibrating the rigid porous body at an ultrasonic frequency.

As will be described below, such a method and generator is particularly suitable for the aerosol delivery of biopharmaceuticals since the method and apparatus produce low stresses in the particles of the aerosol, and also permit close control of the particles size distribution in the produced aerosol. When the method and apparatus are to be used for the aerosol delivery of biopharmaceuticals, the liquid introduced in the reservoir is preferably a mixture of the biopharmaceutical and a liposome in a buffered solution.

Further features and advantages of the invention will be apparent from the description below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 is a block diagram illustrating one form of aerosol generator constructed in accordance with the present invention;

Fig. 2 is a block diagram illustrating modifications in the construction of the aerosol generator of Fig. 1; and

Fig. 3 and Fig. 4 are block diagrams illustrating two further modifications int he construction of the aerosol generator.

DESCRIPTION OF PREFERRED EMBODIMENTS

The aerosol generator illustrated in Fig. 1 comprise a reservoir 2 provided with a rigid microporous body 3 and a piezoelectric device 4. The rigid microporous body 3 is in the form of a layer secured within reservoir 2 slightly raised from its bottom wall 2a, so as to define a chamber 5 above the microporous layer 3, and another chamber 6 below the microporous layer. Reservoir 2 is provided with an inlet, shown at 7 in a top wall 2b for inletting the liquid to be nebulized, and with an outlet 8 for outletting the nebulized liquid in the form of a small-particle aerosol. When the nebulized liquid is a pharmaceuthical, e.g., to be inhaled by a patient, outlet 8 includes a face mask 9 to be applied over the face of the patient.

The piezoelectric device 4 is in contact with the rigid microporous layer 3 so as to vibrate that layer by ultrasonic vibrations. Piezoelectric device 4 is driven by an electrical power supply, schematically shown by block 10, under the control of a control circuit, schematically shown by block 11.

Chamber 6 underlying the rigid microporous layer 3 within reservoir 2 includes an inlet 12 for inletting the compressed air into chamber 6. The compressed air is supplied by a compressor 13 via a conduit 14 and is also under the control of the control circuit 11.

The liquid to be nebulized is introduced via inlet 7 into chamber 5 so as to contact the upper face of the rigid microporous layer 3, whereas the compressed air is introduced into chamber 6 so that it is applied to the lower face of the rigid microporous layer 3. Accordingly, when the piezoelectric device 4 is driven at ultrasonic frequencies, the vibrations produced by it, as applied to the microporous layer 3, generate a small-particle aerosol within chamber 5 which is outletted via the outlet 8.

The frequency and intensity at which the piezoelectric device 4 is driven by the driving unit 10, and the rate of air flow from the compressor 13, can be controlled to provide the desired particle size, particle size distribution, and flow rate in the produced aerosol. In addition, the shear stresses in the particles in the produced aerosol are relatively low as compared to the other known techniques briefly described above. These advantages make the described generator particularly useful for the aerosol delivery of biopharmaceuticals. In such cases, the liquid within chamber 5 would be the desired pharmaceutical to be delivered mixed with a liposome in a buffer solution, as known in this art.

The control circuit shown by block 11 in Fig. 1 could be a personal computer. The parameters concerning the aerosol to be delivered (e.g., particle size, delivery rate, delivery period, etc.) can be inputted into the computer to control the piezoelectric driver 10, and the air compressor 13, to obtain the desired results. Preferably, the piezoelectric driver 10 would be operated within the range of from 10 to 100 KHz, with an output power of from 100 milliwatts to a few watts. The microporous layer 3 is preferably a microporous ceramic or glass, but could also be a microporous metal. Preferably, the pores are of micron size, up to several hundred microns.

Instead of using a separate piezoelectric unit 4 for vibrating the rigid microporous layer 3, the microporous

layer may incorporate piezoelectric material within it. For example, a porous ceramic material may be imparted with piezoelectric properties by incorporating piezoelectric material within a porous matrix of the ceramic and integrating it into a rigid microporous body. Techniques for accomplishing the foregoing are known, as described in Ting, PIEZOELECTRIC PROPERTIES OF A POROUS PZT CERAMIC, Ferroelectric, 1985, Vol.65., pp.12-20; Kahn et al, PREPARATION AND PIEZOELECTRIC RESPONSE OF PZT CERAMICS WITH ANISOTROPIC PORES, Advanced Ceramic Materials, Vol.1, (1) 1996, p.33; and the references cited in such articles.

Fig. 2 illustrates an aerosol generator including such a rigid microporous body incorporating piezoelectric material within it, rather than providing a separate piezoelectric device in contact with the rigid microporous body. Thus, the generator illustrated in Fig. 2 includes a reservoir 22 containing the integrated rigid microporous body 23 incorporating the piezoelectric material within it, and dividing the interior of the reservoir into an upper liquid compartment 25 and lower air compartment 26. The other elements in Fig. 2 common with those described above in Fig. 1 carry the same reference numerals to facilitate understanding the construction and operation of the generator of Fig. 2.

The generator of Fig. 2, however, includes several other modifications. One such modification is the addition of an air supply inlet 35 for inletting drying air into chamber 25 above the liquid being nebulized, to remove water from the aerosol which is discharged from outlet 8. Another modification is the provision of a heater 36 in the outlet conduit 8 also for removing water from the discharged aerosol. In addition, the air generator illustrated in Fig. 2 includes a flow meter 37 in the conduit 14 supplying air from compressor 13 into the air chamber 26 of the reservoir 22.

Fig. 3 illustrates a generator similar to that of Fig. 1, except the piezoelectric device 34 is attached directly to the reservoir 2; and Fig. 4 illustrates a similar generator except the piezoelectric device 44 is submerged within the liquid in the reservoir 2.

In all other respects, the generators illustrated in Figs. 2, 3 and 4 are constructed and operate in the same manner as described above with respect to Fig. 1.

While the invention has been described with respect to several preferred embodiments, it will be appreciated that these are set forth merely for purposes of examples, and that many other variations, modifications and applications of the invention may be made.

WHAT IS CLAIMED IS:

1. A method of nebulizing a liquid to produce a small-particle aerosol, comprising:

providing a reservoir with a rigid porous body;

introducing liquid to be nebulized into the reservoir to contact the upper face of said rigid porous body;

introducing a pressurized gas to be applied to another face of said rigid porous body;

and vibrating said rigid porous body at an ultrasonic frequency.

2. The method according to Claim 1, wherein said rigid porous body is a microporous body having pores of up to several microns in size.

3. The method according to Claim 2, wherein said rigid porous body is a ceramic.

4. The method according to Claim 2, wherein said rigid porous body is glass.

5. The method according to Claim 2, wherein said rigid porous body is a metal.

6. The method according to Claim 1, wherein said rigid porous body is vibrated by a piezoelectric mechanism.

7. The method according to Claim 6, wherein said rigid porous body is vibrated by a piezoelectric device in contact with the rigid porous body.

8. The method according to Claim 6, wherein said rigid porous body is vibrated by piezoelectric material incorporated in a porous matrix and integrated into said rigid porous body.

9. The method according to Claim 8, wherein said porous matrix is a ceramic.

10. The method according to Claim 6, wherein said rigid porous body is vibrated by a piezoelectric device attached to said reservoir.

11. The method according to Claim 6, wherein said rigid porous body is vibrated by a piezoelectric device submerged in the liquid in said reservoir.

12. The method according to Claim 1, wherein said rigid porous body is vibrated at a frequency of 10-100 KHZ.

13. The method according to Claim 1, wherein: said rigid porous body is in the form of a layer in said reservoir, said liquid is introduced into contact with the upper face of said rigid porous layer, and said pressurized gas is applied to the lower face of said rigid porous layer.

14. The method according to Claim 1, wherein said gas is air.

15. The method according to Claim 1, wherein said reservoir is closed except for inlets for the liquid and pressurized gas and an outlet at the upper end of the reservoir through which the small-particle aerosol is outletted; and wherein a drying gas is also introduced into the upper end of the reservoir above the liquid therein.

16. The method according to Claim 1, wherein the frequency and intensity of the vibrations are controlled to control the size distribution and output rate of the aerosol particles.

17. The method according to Claim 16, wherein the aerosol particles range from a size of 0.5um to 10um.

18. The method according to Claim 1, wherein the liquid introduced into the reservoir is a mixture of a biopharmaceutical and a liposome in a buffer solution.

19. The method according to Claim 1, wherein the produced aerosol is heated as it is outputted from the reservoir to remove water from the aerosol.

20. An aerosol generator for nebulizing a liquid to produce a small-particle aerosol, comprising:

a reservoir for receiving liquid to be nebulized;

a rigid porous body within the reservoir;

a liquid inlet for introducing liquid to be nebulized into the reservoir to contact the upper face of the rigid porous body therein;

a source of pressurized gas for introducing a pressurized gas into the reservoir to be applied to another face of said rigid porous body;

and a vibrator for vibrating said rigid porous body at an ultrasonic frequency.

21. The generator according to Claim 20, wherein said rigid porous body is a microporous body having pores of up to several microns in size.

22. The generator according to Claim 21, wherein said rigid porous body is in the form of a rigid porous layer in said reservoir, said liquid is introduced into contact with the upper face of said rigid porous layer, and said pressurized gas is applied to the lower face of said rigid porous layer.

23. The generator according to Claim 22, wherein said vibrator is a piezoelectric device.

24. The generator according to Claim 23, wherein said piezoelectric device is in contact with said another face of said rigid porous body.

25. The generator according to Claim 23, wherein said piezoelectric device is in a form of piezoelectric material incorporated in a porous matrix integrated into said rigid porous body.

26. The generator according to Claim 25, wherein said porous matrix is a ceramic.

27. The generator according to Claim 23, wherein said piezolecetric device is attached to said reservoir.

28. The generator according to Claim 23, wherein said piezoelectric device is submerged in the liquid in said reservoir.

29. The generator according to Claim 20, wherein said generator further includes a control system for

controlling the frequency and intensity of vibrations by said vibrator to control the particle size distribution and/or the output rate of the produced aerosol.

30. The generator according to Claim 29, wherein said source of pressurized gas includes a compressor, and said control system also controls said compressor to control the pressure and/or output rate of the pressured gas introduced into said reservoir.

31. The generator according to Claim 20, wherein said reservoir is closed except for inlets for the liquid and the pressurized gas and an outlet at the upper end of the reservoir through which the small-particle aerosol is outletted; and wherein said reservoir also includes a further inlet for introducing a drying gas into the upper end of the reservoir above the liquid therein.

32. The generator according to Claim 20, wherein said aerosol outlet includes a heater for removing water from the outleted aerosol.

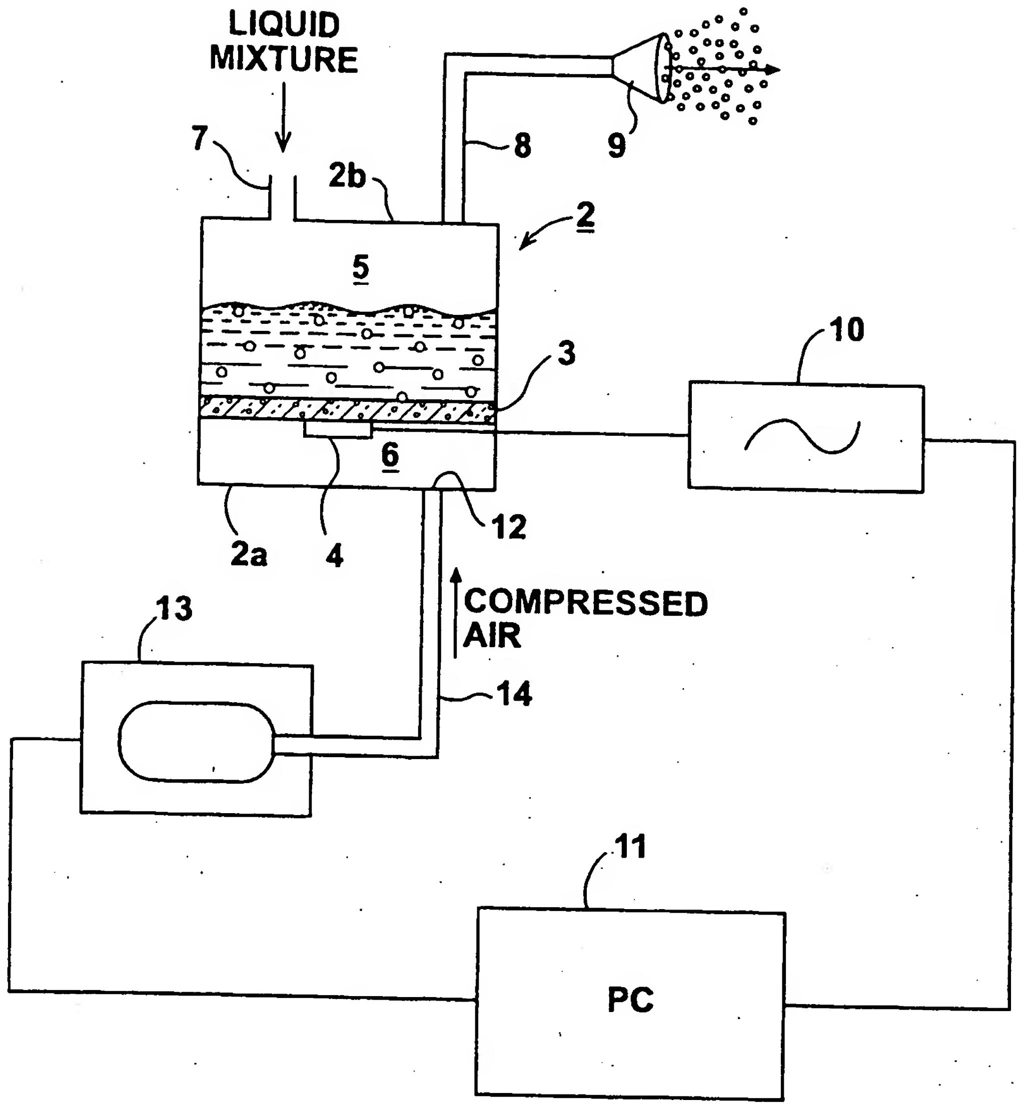
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FIG. 1

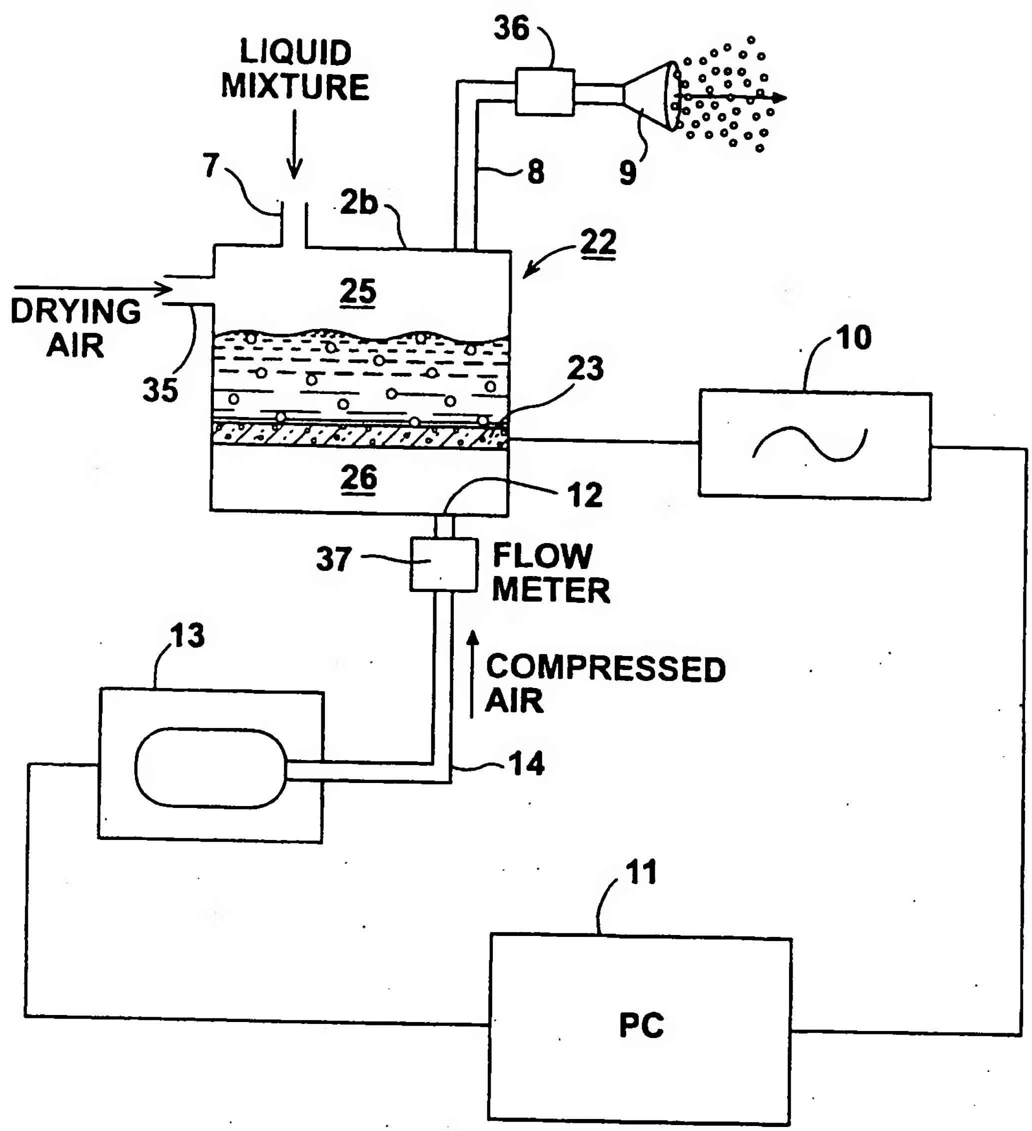
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FIG. 2

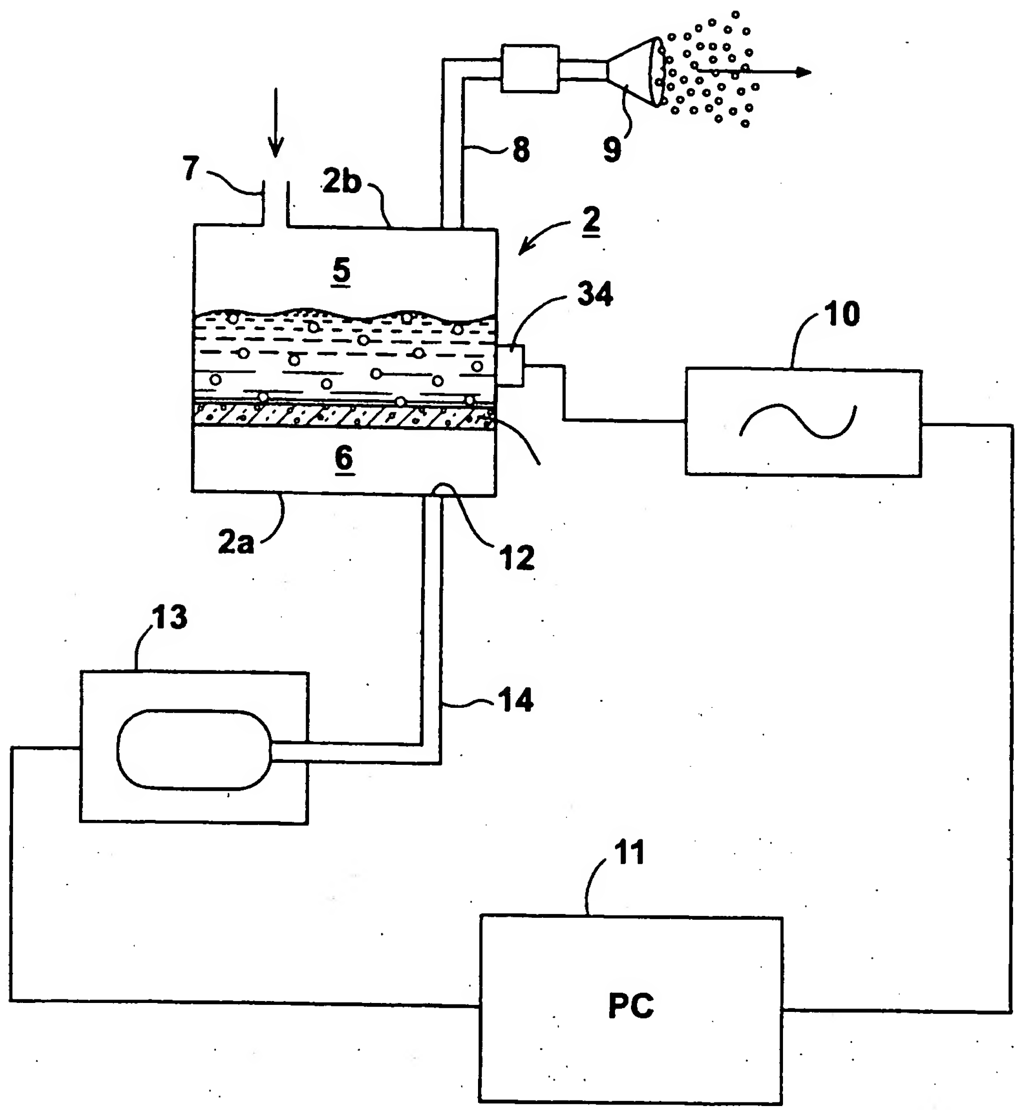

FIG. 3

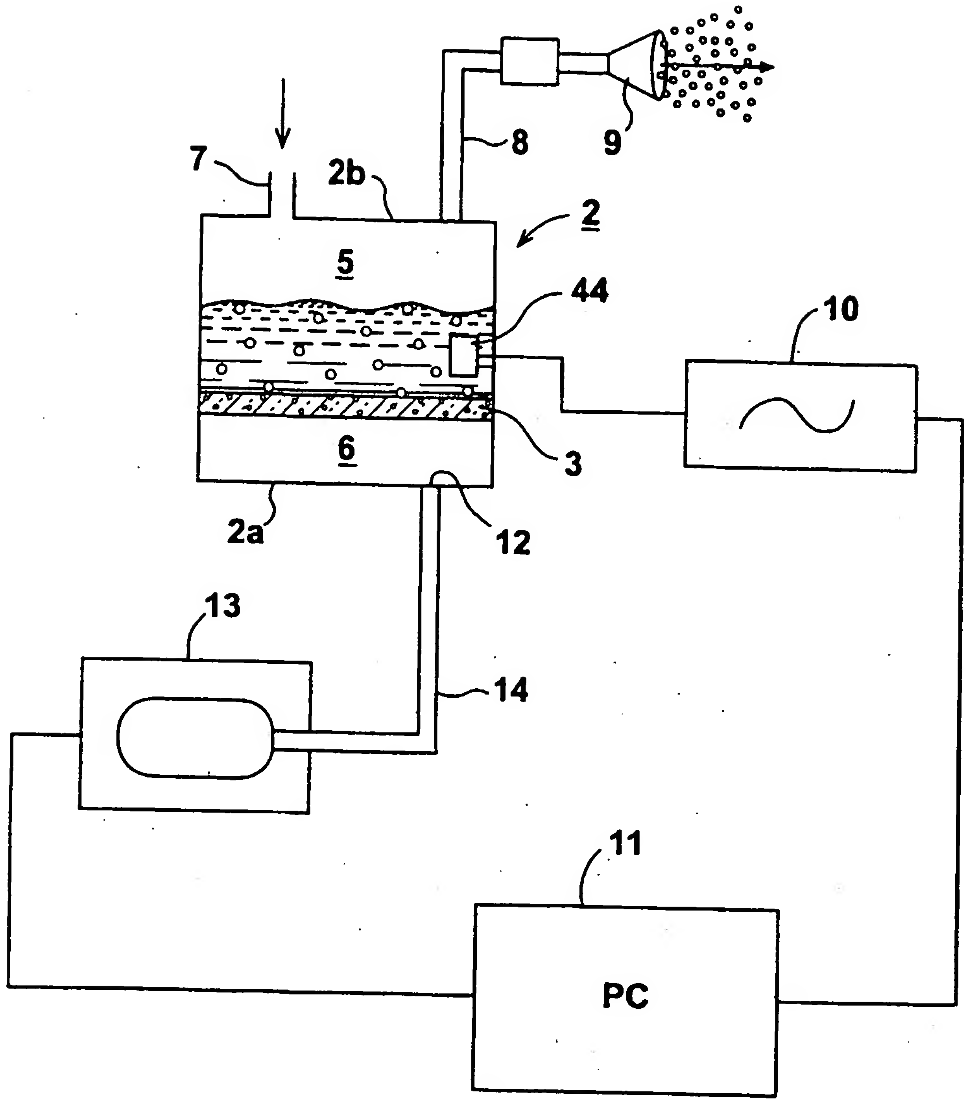

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL00/00181

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : B05B 17/04
US CL : 239/4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 239/4, 102.1, 102.2, 134, 311, 337, 338, 372; 261/122.1, 81, DIG48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 4,793,714 A (GRUBER) 27 DECEMBER 1988, see entire document	1, 13, 16, 20, 22, 29 ---------- 2-10, 11, 12, 14, 15, 17, 19, 21, 23-28, 30-32
A	US 3,790,079 A (BERGLUND ET AL) 05 FEBRUARY 1974, see entire document	1, 20
A	US 4,087,495 A (UMEHARA) 02 MAY 1978, see entire document	1, 20

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 4,708,826 A (MIZOGUCHI) 24 NOVEMBER 1987, see entire document	2-10, 12, 14, 15, 17, 19, 21, 23-27, 30-32
Y	US 3,918,640 A (PICCINO ET AL) 11 NOVEMBER 1975, see entire document	11, 28